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(54) Title: SKIN AND NAIL COMPOSITION CONTAINING PHOSPHATE-TRIALKANOLAMINE COMPLEX

(57) Abstract

Topical medicaments and skin and nail preparations which comprise a phosphatide component (a) and an ethanolamine component (b). In the skin and nail embodiments there is no necessity for any additional third component, although additional ingredients may be included. In the topical medicament embodiment, there are three components, the invention as to topical medicaments being a preparation for application to the skin of a patient which contains a drug capable of passing through said skin to provide topical relief to said patient for the purpose for which said drug is administered, said topical medicament comprising a mixture of: (a) at least about 1% by weight of a lecithin-containing phosphatide, the amount of lecithin in said phosphatide being about 10% to about 40% by weight; (b) at least about 0-2% by weight triethanolamine; and (c) a drug suitable for topical administration, said topical medicament providing said drug suitable for topical administration in a form to permit retention of said drug at the skin of said patient to whom said drug being applied and protecting the skin area due to the presence of a complex of the components (a) and (b).

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SKIN AND NAIL COMPOSITION CONTAINING PHOSPHATE-
TRIALKANOLAMINE COMPLEXTOPICAL MEDICAMENT

The present invention provides a topical mode of applying drugs, including steroids and also drugs to clear up or prevent local skin conditions such as eczema. Critical to the present invention is the combination of the drug with a phosphatide that includes lecithin. In one preferred embodiment, triethanolamine is also included. In the skin preparation of the present invention the drugs are retained for a long period of time, permitting a prolonged dispersal of the drug.

The phosphatides which can be used in the skin preparation of this invention include phosphatidyl choline (lecithin), phosphatidyl ethanolamine (cephalin), phosphatidyl serine, phosphatidyl inositol and phosphatidic acid. A mixture of the above phosphatides can also be used. Optimally the phosphatide should contain 10 to 40% lecithin.

It is advantageous to use a commercially available lecithin containing a phosphatide mixture and especially soy phosphatide (soy lecithin and egg phosphatide (egg lecithin) as the mixture of the phosphatides. Such commercially available phosphatides contain various phosphatides and other components.

The amount of the phosphatides which are used in the skin preparation of this invention varies with the condition or symptom to be treated, the formulation, and the kind and amount of the topically delivered drugs contained in the skin preparation. However, the amount of the phosphatides is normally in the range of 0.5 to 8% by weight, and preferably 1.5 to 5% by weight. If the phosphatide is used in too small amounts, the beneficial effects of this invention will be insufficient. The effect of the skin preparation attained when the phosphatide is used in an excessive amount is not proportional to the amount of the phosphatide to be used, because the skin cannot

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absorb the excessive amount of the phosphatide. In addition, the use of the excessive phosphatides causes stickiness. Therefore, in general, a not more than 5% composition will be satisfactory.

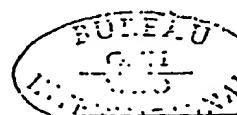
While in the generic aspect of the invention lecithin may be used by itself with drug, in an embodiment trialkanolamines are used that may complex with the lecithin. Particularly, substituted and hindered trialkanolamines are considered such as triethanolamine and triisopropanolamine. The alkanolamine can be used in an amount of 0.2 to 25 moles per mole of the phosphatide, preferably 1 to 10 moles, and more preferably 1.5 to 5 moles are used.

Depending upon the intended use of the skin preparation of this invention, other components can be incorporated into the skin preparation of this invention to prepare the skin preparation having various rheological properties.

For such formulations there can be used an aqueous mixture such as a solution, colloidal solution, emulsified lotion, oil-in-water cream (hydrophilic cream) and aqueous gel wherein the aqueous phase is the continuous one.

For such formulations, there can also be used an oily mixture such as a solution, ointment, water-in-oil cream, gel base (e.g. Plastibase, a polyethylene and liquid petrolatum base), absorption base and hydrophilic ointment wherein the oil phase is the continuous one and a nonaqueous water-soluble base such as a mixture of polyethylene glycol. Such water-in-oil formulations are especially useful in preventing transdermal water loss and serve as effective carriers for transdermal drug delivery.

A suspension base such as a shaking lotion, in which a solid dispersing agent is added, can also be prepared. Oily components, emulsifiers, dispersing agents,



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gelatinizers and solid materials which can be used to prepare such formulations are well known, as those used are in the preparation of cosmetics and topical products.

The oily components include hydrocarbons such as liquid paraffin, petrolatum, solid paraffin, microcrystalline wax and the like; higher aliphatic alcohols such as cetyl alcohol, hexadecyl alcohol, stearyl alcohol, oleyl alcohol and the like, esters of higher aliphatic alcohols such as bees wax, spermaceti and the like; esters of higher aliphatic acids with lower alcohols such as isopropyl myristate, isopropyl palmitate and the like, vegetable oils, modified vegetable oils, anhydrous lanolin and its derivative, squalene, squalane and the like. Higher aliphatic acids such as palmitic acid, stearic acid and the like can also be used. However, they should be used in a smaller amount, since they form a soap with alkanolamine.

Useful emulsifiers and dispersing agents include anionic, cationic and nonionic surfactants. Nonionic surfactants are preferred because of their low level of irritation to skin. Typical of nonionic surfactants are monoglycerides such as glyceryl monostearate and the like; sorbitan aliphatic esters such as sorbitan monolaurate and the like; sucrose aliphatic esters; polyoxyethylene aliphatic esters such as polyoxyethylene stearate; and polyoxyethylene cetyl ether, polyoxyethylene oleyl ether, polyoxyethylene fatty ethers and the like.

Gelatinizers include carboxymethylcellulose, cellulose gel, carbopol (carboxypolymethylene), polyvinyl alcohol, polyethylene glycol and various gums.

These oily components, emulsifiers, dispersing agents and gelatinizers can be used alone or in combination with each other.

The incorporation into the skin preparation of this invention of propylene glycol, glycerine, sorbitol or

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the like which have moisturizing action is preferred, because it enhances moisturizing action of the skin preparation of this invention.

Ethanol may be provided as a component of the skin composition, ethanol having bacteriostatic action and providing a cooling effect upon application to the skin.

In order to increase the stability of the skin preparation of this invention and/or the drugs contained therein, it is preferred to add antioxidants, chelating agents, antiseptics and the like, if necessary. The antioxidants include butylated hydroxytoluene, butylated hydroxyanisole, tocopherol, sodium pyrosulfite, acetone sodium bisulfate and the like. The chelating agents include ethylenediaminetetraacetic acid, thioglycolic acid, thiolactic acid, thioglycerol and the like.

The suitable antiseptics include methyl, ethyl, propyl and butyl esters of p-hydroxybenzoic acid, o-phenylphenol, dehydroacetic acid and the salts thereof, p-chloro-m-cresol, p-chloro-m-xyleneol and the like.

In addition, it is preferred to adjust the pH of the skin preparation of this invention by adding citric acid, lactic acid, tartaric acid or the like. The pH value which should be adjusted to is dependent upon the stability of the skin preparation. In general, it is preferred that the skin preparation be slightly acidic to slightly alkaline.

A fragrance may be added in a slight amount, if desired.

When the skin preparation of this invention is used for the delivery of drugs, the action of the drugs is strengthened, because the dispersion and retention in the skin of the drugs are enhanced to a considerable extent and pressure of the drugs maintained for a long period of time. Thus in the case of many steroids there appears to occur a complexing with the phosphatide

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causing uniform distribution and release over the skin surface.

Any drugs which are applicable to the skin can be used in the skin preparation of this invention. Examples of such drugs are topical steroid hormones such as hydrocortisone, prednisolone, methylprednisolone, dexamethasone, triamcinolone, triamcinolone acetonide, flumethasone, fluocinonide, beclomethasone, betamethasone, fluocinolone, fluorometholone, fludoxycortid, clometasone, clobetazol and their esters.

Other drugs which can be applied to the skin preparation of this invention include topical antibiotics such as kanamycin, erythromycin, tetracycline, gentamycin, fradiomycin, chloramphenicol and their salts; anti-mucotic agents such as griseofulvin, siccanin, trichomycin, nystatin, silver sulfadiazine, and the like; topical sulfa drugs such as sulfisoxazole and the like; topical antihistamines such as diphenhydramine, chlorphenilamine and the like; local anesthetics such as lidocaine, dibucaine, cyproheptazine and cocaine; non-steroidal antiinflammatory agents such as indomethacin, diflumidone, bufexamac and the like; anticoagulants such as heparin sodium; skin keratolytic agents such as urea, salicylic acid, resocinol, coal tar, anthralin and the like; agents affecting pigmentation such as methozalen and the likes; vitamins such as vitamin A, vitamin E and the like; sex hormones such as ethinyl estradiol, testosterone, progesterone and the like; antianginal drugs such as isosorbide dinitrate, nitroglycerin, verapamil, prenilaramine and the like; beta-blocking agents such as propranolol, pindolol, alprenolol and the like; antihypertensive agents such as fydralazine, reserpine, clonidine and the like and bronchodilators such as isoproterenol, meta-proterenol and the like; antiallergic agents such as cromolyn sodium and the like and antiserotonergic agents

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such as cyproheptazine.

The opical steroid hormone can be applied in combination with one or more drugs of topical anticiotics, antihistaminics and antimycotic agents.

Anticancer drugs such as tetrahydrofluorouracil, fluorouracil, bleomycin, mitomycin and the like can also be applied to the skin preparation of this invention.

The amount of the drugs to be added to the skin preparation should be determined on the basis of the activity of the drugs. When a larger amount of the drug is used, it is preferred to increase the amounts of the phosphatide and the alkanolamine to be used.

A drug can be added to the skin preparation either in the form of a solution in the oily components, water, propylene glycol, polyethylene glycol or ethanol, or in the form of a solid as it is or as pulverized powder.

The symptoms of patients with dry skin condition disappear or are alleviated by application of the skin preparation of this invention.

The skin preparation of this invention containing a topical steroid hormone can be used to treat eczema, ichthyosis, lichen psoriasis and the like to attain the disappearance or alleviation of the symptom. As described above, the skin preparation of this invention has the action of moisturizing and tenderizing skin and nail. In addition, the skin preparation of the invention, when used for the delivery of drugs, disperses and retains the drugs in the skin in a uniform manner. Therefore, the skin preparation of this invention is very useful for moisturizing skin, preventing keratinization, tenderizing nail and treating skin diseases.

Beyond the general description of this invention, a more complete understanding can be obtained by examples which are provided herein for purposes of illustration only and are not intended to be limiting in any manner.

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A. OLEAGINOUS OINTMENT(A-1) Ointments prepared from petrolatum

White petrolatum was melted on a water bath and warmed to about 70°C. The other ingredients were dispersed in the liquid paraffin and warmed to 70°C and then added to the petrolatum and was stirred until it congealed.

(A-2) Ointments prepared from Plastibase

All of the components are combined and stirred to obtain a uniform mixture.

B. POLYETHYLENE GLYCOL OINTMENT

Polyethylene glycol 400 was heated on a water bath at 60 to 70°C. Polyethylene glycol 400 and the other ingredients, previously dispersed in the liquid paraffin, were added to this melt with stirring. Stirring was continued until the solidification takes place.

C. ABSORPTION OINTMENT

Cetyl alcohol and white petrolatum were melted on a water bath, then the other ingredients were added to this melt and the mixture was heated to about 75°C with stirring. Next, the deionized water was heated to the same temperature and added. The mixture was stirred until it congealed.

D. OIL-IN-WATER CREAM (HYDROPHILIC OINTMENT)

Stearyl alcohol, cetyl alcohol, polyoxyethylene 45 monostearate and white petrolatum were melted on a water bath, then the other ingredients were added to this melt and the mixture was heated to about 75°C with stirring. Next, the deionized water was heated to the same temperature and added. The mixture was stirred until it congealed.

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Example 1 Oil-In-Water Cream

The following skin preparation was made:

White petrolatum	9.9% by weight
liquid paraffin	12.9
stearyl alcohol	5.0
Cetyl alcohol	2.1
SLP-White (powdery soy lecithin having a phos- phatide content of 95%)	4.0
Triethanolamine	0.8
Citric acid monohydrate	0.35
Dibutyl hydroxytoluene	0.025
Polyoxyethylene 1000	
cetyl ether	4.0
p-Chloro-m-cresol	0.2
Deionized water	<u>remainder</u>
	100%

The above skin preparation has been tested on the skin and found to provide a good moisturizing effect. The moisture barrier provided by the relatively large molecular complex (each mole of lecithin capable of complexing tightly with 10 to 12 molecules of water) and the lecithin staying near the surface due to the positively and negatively charged portions of the molecule, the skin preparation of the present invention provides relatively long protection for the skin against drying. Varying the ratio of triethanolamino to a phosphatide, tests have been made. Most advantageous effects have been found for 1 to 4 moles of triethanolamine per mole of a phosphatide.

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EXAMPLES 2 to 5

The following skin preparations were made:

EXAMPLE No.	o/w cream	Oleaginous Ointment	Polyethylene	
			Glycol Ointment	Absorbtion Ointment
Composition	2	3	4	5
SLP-White				
(Soybean lecithin)	4.0	4.0	4.0	4.0
Triisopropanolamine	1.0	1.0	1.0	1.0
Lactic Acid	0.58	0.58	0.58	0.58
Butylated				
hydroxytoluene	0.025	0.025	0.025	0.025
White petrolatum	9.9	-	10.0	40.0
liquid paraffin	12.9	-	-	-
Plastibase 50 W				
(polyethylene and				
liquid petrolatum base)	-	94.395	-	-
Stearyl alcohol	5.0	-	-	-
Cetyl alcohol	2.1	-	-	18.0
Polyethylene glycol				
4000	-	-	41.395	
Sorbitan Sesquioleate	-	-	-	5.0
Polyoxyethylene 45				
Monostearate	4.0	-	-	-
Polyoxyethylene lauryl				
ether	-	-	-	0.5
p-Chloro-m-cresol	0.2	-	-	0.2
Deionized water	60.745	-	-	30.695
Total (% by weight)	100.0	100.0	100.0	100.0

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Using these skin preparations, transepidermal water loss experiments were made.

- I. Skin samples are obtained from fresh cadavers. All skin samples are from the abdominal area. Epidermis is separated from dermis by the procedure of Baumberger (J. of Natl. Cancer Inst. (US) 2, 413, 1941). Epidermal samples are wrapped in aluminum foil and are maintained at -20° until used.
- II. Apparatus for transepidermal water loss is all glass with ground glass joints to secure the epidermis. The opening in the apparatus over which the epidermis is placed occupied 2 cm^2 . All of the apparatus is inside an analytical balance. The balance chamber contains a humidity controller. Weight measurements are made as a function of time. Epidermal samples, about 2 cm on a side, are placed onto the water reservoir portion of the TWL apparatus. The open cover of the apparatus is clipped into place with the epidermis clamped between the ground glass surfaces. The apparatus containing the epidermal sample and water is weighted. Thirty minutes are allowed for evaporation of surface water before measurements begin. Gravimetric measurements allow for determinations of water loss to be made. 2-4 hours are required for steady state to be achieved. Measurements continue for several hours after steady state has been achieved. The steady state rate at the 15th hour from the start of the measurement is used as the transdermal water loss rate.

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The following skin preparations were used as references:

Composition	Comparative Skin Preparation		
	A	B	C
	o/w Cream Oleaginous Ointment		
White petrolatum	9.9	-	100
Liquid paraffin	12.9	-	-
Plastibase 50W	-	100	-
Stearyl alcohol	5.0	-	-
Cetyl alcohol	2.1	-	-
Polyoxyethylene cetyl ether	1.7	-	-
P-Chloro-M-Cresol	0.1	-	-
Deionized water	68.3	-	-
Total (% by weight)	100.0	100.0	100.0

The results are shown in the following table:

Skin Preparation		Rate of Epidermal Water Loss (mg H ₂ O/cm ² -hour) (at the 15th hour from the start of the experiment)
Untreated epidermal sample		0.49
lipid extracted material		1.0
carried out with CHCl ₃ /MeOH		
Skin Preparation A		0.44
"	B	0.065
"	C	0.060
Skin Preparation 2		0.25
"	3	0.041
"	4	0.055
"	5	0.13

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The transepidermal water loss (TWL) values represent averages of 3 sets of values carried out on 3 different samples of epidermal skin for each condition. The data obtained with lipid extracted material (carried out with chloroform-methanol) demonstrate that the water loss through epidermis is substantially enhanced. This indicates that the barrier to water loss by epidermis and by stratum corneum is substantially determined by lipid content. The untreated sample drops to a half value. The rate of epidermal water loss of the epidermal skin sample treated with the conventional skin preparation decreases as the water content of the skin preparation decreases. Although a decrease in the rate of epidermal water loss of the epidermal skin sample treated according to this invention is accompanied by a decrease in the water content of the skin preparation, the decrease is always smaller than that of the conventional skin preparation compared at the same water content. This demonstrates that phosphatide and triisopropanolamine contained in the skin preparation of this invention suppress the water loss.

EXAMPLES 6, 6', 6'', 7, 7', and 8:

Topical steroid hormone skin preparations having the following composition were prepared.

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EXAMPLE NO. Composition	Example 6	Example 6'	Compara- tive D	Example 7	Compara- tive E	Example 8	Compara- tive F
Beclomethasone 17,21-dipropionate	0.025		0.025				-
Hydrocortisone	-		-	1.0			-
Prednisolone	-		-				1.0
SLP-White	4.0	4.0	/	4.0	/	4.0	/
Triethanolamine	0.8	0.8		0.8		0.8	
Lactic acid	0.62	0.62		0.62		0.62	
Butylated Hydroxytoluene	0.025	0.025		0.025		0.025	
White petrolatum	9.9	-		40.0		-	
Liquid paraffin	12.9	-		-		10.0	
Plastibase 50 W	-	94.53		-		-	
Stearyl alcohol	5.0	-		-		-	
Cetyl alcohol	2.1	-		18.0		-	
Polyoxyethylene glycol 4000	-	-		-		-	
Polyoxyethylene glycol 400	-	-		-		46.55	
Polyoxyethylene glycol 45-monoacetate	4.0	-		-		37.0	
Gorhitan sesquiolate	-	-		5.0		-	
Polyoxyethylene lauryl ether	-	-		0.5		-	
p-Chloro-m-cresol	0.2	-		0.2		-	
Deionised water	60.43	-		29.855		-	
Total (% by weight)	100.00	100.00	100.00	100.00	100.00	100.00	100.00

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The Toneli method was used to measure the anti-inflammatory activity of this skin preparation [Endocrinology 77 625-634 (1965)]. A phlogistic solution comprising pyridine, ether and croton oil (50:45:5 V/V) is applied to the right ear of the mouse and then the skin preparation is applied thereon. Five hours after the treatment, both of the ears are excised at a predetermined position and the wet weight of the ears are determined to calculate the edema ratio according to the following equation:

$$\text{Edema Ratio (\%)} = \left(\frac{\text{Weight of Right Ear}}{\text{Weight of Left Ear}} - 1 \right) \times 100$$

Inhibition ratio is calculated according to the following equation:

Inhibition Ratio (%)

$$= \left(1 - \frac{\text{Edema ratio when treated with ointment}}{\text{Edema ratio when untreated}} \right) \times 100$$

Ten male mice weighing 20 to 25 g are used as one group. The results are shown in the following table.

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Drug	Preparation	Edema Ratio	Inhibition	Effect*
	%	Ratio (%)		
	Example 6	22.9	77.9	+++
Beclomethasone	Example 6	23.1	77.7	+++
17, 21-dipropionate	Comparative D	32.8	68.4	++
	Example 7	39.1	62.3	++
Hydrocortisone	Comparative E	45.1	56.5	++
	Example 8	35.7	65.5	++
Prednisolone	Comparative F	40.2	61.2	++
Untreated		103.6	0	-

*	Score	Inhibition Ratio
	+++	75-100%
	++	50-75%
	+	25-50%
	-	0-25%

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As is apparent from the above table, the skin preparation of this invention possesses higher anti-inflammatory activity as compared with the conventional ointment bases. Judging from these results, the pharmaceutical effects of the skin preparation of this invention are raised by the formation of a complex in which a phosphatide is non-covalently complexed with a steroid, because the complex increases the compatibility and retainability of the steroid in the skin.

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EXAMPLES 9, 10 and 10'

The skin preparation having the following composition are prepared.

	Oleaginous Ointment		o/w cream		Absorption Ointment
Example No.	Example	Compara- tive	Example	Compara- tive	Example
Composition	(9)	(G)	(10)	(H)	(10')
Hydrocortisone					
17-butylate	0.1	0.1	-	-	-
Indomethacin	-	-	1.0	1.0	1.0
SLP-White	4.0	-	4.0	-	4.0
(Soy lecithin)					
Triisopro- panolamine	1.0	-	1.0	-	1.0
Lactic acid	0.58	-	0.58	-	0.58
Butylated hydroxytoluene	0.025	-	0.025	-	0.025
White Petrolatum	-	-	9.9	9.9	40.0
Liquid paraffin	-	-	12.9	12.9	-
Plastibase 50W	94.292	99.9	-	-	-
Stearyl alcohol	-	-	5.0	5.0	-
Cetyl alcohol	-	-	2.1	2.1	18.0
Polyoxyethylene 45-monostearate	-	-	4.0	4.0	-
p-Chloro-m- cresol	-	-	0.2	0.2	0.2
Deionized water	-	-	qs	qs	29.695
Sorbitan sesquioleate	-	-	-	-	5.0
Polyoxyethylene lauryether	-	-	-	-	0.5
Total (w/w%)	100.0	100.0	100.0	100.0	100.0

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Anti-inflammatory activity is measured for the above skin preparations by skin carrageenan edema inhibition test. The test is conducted by the following method.

Male rats weighing 190-210 g are used in the following test. Their side abdominal hair is removed before the start of this test. 1% carrageenin solution is injected intra-dermally at a predetermined position from each side of the abdomen. Immediately after carrageenin injection, 1 ml of 1% pontamine sky blue saline is administered intravenously. Furthermore, an accurately determined volume of topical formulation is applied on the surface of the abdominal skin.

Five hours after the treatment, the abdominal skin is removed from the body and score as to the following items.

Dye leakage at the injection site

Calculated by measuring the maximum and minimum diameter of the dye blue spot.

Edema skin weight

Calculated by measuring the weight of the perforated edema skin (1cm x 1cm = round shape)

Edema weight = Edema skin weight - Normal skin weight

Edema ratio = Edema weight / Normal skin weight

The results are shown in the following table.

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Hydrocortisone 17-alpha-butyrate - 0.1%

	Example (9)	Comparative (G)	Untreated
Edema weight (mg)	58.4 (-47.7%)	72.9 (-34.7%)	111.7 (-)
Edema ratio	79.4 (-44.4%)	99.7 (-30.2%)	142.8 (-)
Blue area (mm ²)	68.7 (-44.3%)	79.5 (-35.5%)	123.3 (-)
Effect*	++	++	

Indomethacin 1%

	Example (10)	Comparative (H)	Untreated
Edema weight (mg)	51.6 (-23.7%)	62.9 (- 7.0%)	67.6 (-)
Edema ratio	68.9 (-24.1%)	86.9 (- 4.3%)	90.8 (-)
Blue area (mm ²)	72.5 (- 6.9%)	68.2 (-12.5%)	77.9 (-)
Effect*	+	-	

*Score	++	Inhibition ratio	30-45%
	+		15-30%
	-		0-15%

As is apparent from the above table, the skin preparation of this invention possesses higher anti-inflammatory activity as compared with the conventional topical formulations.

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EXAMPLES 11 and 11'

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The skin preparations having the following composition were prepared.

	o/w cream	Absorption Ointment
	Example 11	Example 11'
Chlorpheniramine Maleate	1.0 % by weight	1.0
White petrolatum	9.9	40.0
Liquid paraffin	12.9	-
Stearyl alcohol	5.0	-
Cetyl alcohol	2.1	18.0
SLP-White (Soy lecithin)	4.0	4.0
Triethanolamine	0.8	0.8
Citric acid monohydrate	0.35	0.35
Butylated hydroxytoluene	0.025	0.025
Polyoxyethylene 45-monostearate	4.0	-
p-Chloro-m-cresol	0.2	0.2
Deionized water	qs	30.125
Sorbitan sesquioleat	-	5.0
Polyoxyethylene laurylether	-	0.5
Total (% by weight)	100.0	100.0

The above skin preparation has been tested on the guinea-pig back skin and found to be more effective in preventing vascular permeability increase caused by 0.1% histamine 0.05 ml as compared with the conventional ointment bases.



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EXAMPLES 12-27

Skin preparations are prepared having the composition shown in the following table:

EXAMPLE NO.	Example 12		Example 13		Example 14	
Drug	Sulfisoxazole		Tetracycline Hydrochloride		Chloramphenicol	
	5.0		3.0		2.0	
SLP - White						
(Soy Lecithin)	4.0	4.0	4.0	4.0	4.0	4.0
Triethanolamine	0.8	0.8	0.8	0.8	0.8	0.8
Triisopropanolamine	-	-	-	-	-	-
Lactic acid	0.62	-	0.62	-	0.62	-
Citric acid	-	0.35	-	0.35	-	0.35
Butylated						
hydroxytoluene	0.025	0.025	0.025	0.025	0.025	0.025
White petrolatum	40.0	9.9	86.555	9.9	-	9.9
Liquid paraffin	-	12.9	5.0	12.9	-	12.9
Plastibase 50W	-	-	-	-	92.555	-
Stearyl alcohol	-	5.0	-	5.0	-	5.0
Cetyl alcohol	18.0	2.1	-	2.1	-	2.1
Polyethylene						
Glycol 4000	-	-	-	-	-	-
Polyethylene						
Glycol 400	-	-	-	-	-	-
Polyoxyethylene 45						
monostearate	-	4.0	-	4.0	-	4.0
Sorbitan						
sesquioleate	5.0	-	-	-	-	-
Polyoxyethylene						
laurylether	0.5	-	-	-	-	-
p-Chloro-m-cresol	0.2	0.2	-	0.2	-	0.2
Deionized water	25.855	55.725	-	57.725	-	58.725
Total (% by weight)	100.0	100.00	100.0	100.0	100.0	100.0
Type of Formulation	Absorp- tion ointment	o/w cream	olea- ginuous ointment	o/w cream	olea- ginuous ointment	o/w cream

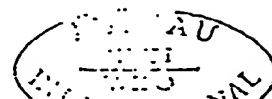
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EXAMPLE NO.	Example 15		Example 16		Example 17
Drug	Gentamicin sulfate 0.1 to 10.0		Acrisorcin 0.2		Ichthammol 10.1
SLP - White (Soy lecithin)	4.0	4.0	4.0	4.0	4.0
Triethanolamine	0.8	0.8	-	-	-
Triisopropanolamine	-	-	1.0	1.0	1.0
Lactic acid	0.62	-	0.58	-	0.58
Citric Acid	-	0.35	-	0.32	-
Butylated hydroxytoluene	0.025	0.025	0.025	0.025	0.025
White petrolatum	-	9.9	40.0	9.9	79.395
Liquid paraffin	10.0	12.9	-	12.9	5.0
Plastibase 50W	-	-	-	-	-
Stearyl alcohol	-	5.0	-	5.0	-
Cetyl alcohol	-	2.1	18.0	2.1	-
Polyethylene Glycol 4000	q.s.-100	-	-	-	-
Polyethylene Glycol 400	42.0	-	-	-	-
Polyoxyethylene 45 monostearate	-	4.0	-	4.0	-
Sorbitan sesquioleate	-	-	5.0	-	-
Polyoxyethylene laurylether	-	-	0.5	-	-
p-Chloro-m-cresol	-	0.2	0.2	0.2	-
Deionized water	-	q.s.-100	q.s.-100	q.s.-100	-
Total (% by weight)	100.0	100.0	100.0	100.0	100.0
Type of Formulation	Polyethyl-ene glycol ointment	o/w cream	Absorp-tionous ointment	o/w cream	Olea-ginous ointment

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EXAMPLE NO.	Example 18		Example 19	Example 20
Drug	Undecylenic Acid 5.0 and Zinc Undecyle- nate 20.0		Nystatin	Sodium Heparin 0.4 (50,000 units)
SLP - White				
(Soy Lecithin)	4.0	4.0	4.0	4.0
Triethanolamine	-	-	0.8	0.8
Triisopropanolamine	1.0	1.0	-	-
Lactic acid	0.58	0.58	0.62	
Citric acid monohydrate	-	-	-	0.35
Butylated hydroxytoluene	0.025	0.025	0.025	0.025
White petrolatum	-	-	40.0	9.9
Liquid paraffin	10.0	-	-	12.9
Plastibase 50W	-	q.s.-100	-	-
Stearyl alcohol	-	-	-	5.0
Cetyl alcohol	-	-	18.0	2.1
Polyethylene Glycol 4000	28.395	-	-	-
Polyethylene Glycol 400	q.s.-100	-	-	-
Polyoxyethylene 45 monostearate	-	-	-	4.0
Sorbitan sesquioleate	-	-	5.0	-
Polyoxyethylene lauryl ether	-	-	0.5	-
p-Chloro-m-cresol	-	-	0.2	0.2
Deionized water	-	-	q.s.-100	q.s.-100
Total (5 by weight)	100.0	100.0	100.0	100.0
Type of Formulation	Polyethylene glycol ointment	Oleaginous ointment	Absorption ointment	o/w cream



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EXAMPLE NO.	Example 21		Example 22		Example 23	
Drug	Urea 10.0		5-Fluoro- uracil 5.0		Bleomycin sulfate 0.5	
SLP - White (Soy lecithin)	4.0	4.0	4.0		4.0	4.0
Triethanolamine						
Triisopropanolamine	1.0	1.0	1.0		1.0	1.0
Lactic acid	0.58	0.58	0.58		0.58	-
Citric acid	-	-	-		-	0.32
Butylated hydroxytoluene	0.025	0.025	0.025		0.025	0.025
White petrolatum	q.s.-100	-	9.9		-	9.9
Liquid paraffin	5.0	-	12.9		10.0	12.9
Plastibase 50W	-	q.s.-100	-		-	-
Stearyl alcohol	-	5.0	5.0		-	5.0
Cetyl alcohol	-	-	2.1		-	2.1
Polyethylene Glycol 4000	-	-	-		42.055	-
Polyethylene Glycol 400	-	-	-		42.0	-
Polyoxyethylene 45 monostearate	-	-	4.0		-	4.0
Sorbitan sesquioleate	-	-	-		-	-
Polyoxyethylene lauryl ether	-	-	-		-	-
p-Chloro-m-cresol	-	-	0.2		-	0.2
Deionized water	-	-	q.s.-100		-	q.s.-100
Total (% by weight)	100.0	100.0	100.0		100.0	100.0
Type of Formulation	Olea- ginous ointment		Olea- o/w ginous cream ointment		Poly- glycol ointment	o/w cream

GENERAL
INTERNATIONAL

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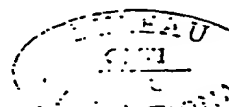
EXAMPLE NO.	Example 24		Example 25		Example 26	
Drug	Lidocaine 3.0		Ethiny- lestoriadiol 0.01		Testosterone 1.0	
SLP - WHITE						
(Soy lecithin)	4.0	4.0	4.0	4.0	4.0	4.0
Triethanolamine	0.8	0.8	0.8	0.8	0.8	0.8
Triisopropanolamine	-	-	-	-	-	-
Lactic acid	0.62	-	0.62	-	0.62	-
Citric Acid	-	0.35	-	0.35	-	0.35
Butylated						
hydroxytoluene	0.025	0.025	0.025	0.025	0.025	0.025
White petrolatum	86.555	9.9	89.545	9.9	-	9.9
Liquid paraffin	5.0	12.9	5.0	12.9	10.0	12.9
Plastibase 50W	-	-	-	-	-	-
Stearyl alcohol	-	5.0	-	5.0	-	5.0
Cetyl alcohol	-	2.1	-	2.1	-	2.1
Polyethylene						
Glycol 4000	-	-	-	-	41.555	-
Polyethylene						
Glycol 400	-	-	-	-	42.0	-
Polyoxyethylene 45						
monostearate	-	4.0	-	4.0	-	4.0
Sorbitan						
sesquioleate	-	-	-	-	-	-
Polyoxyethylene						
lauryl ether	-	-	-	-	-	-
p-Chloro-m-cresol	-	0.2	-	0.2	-	0.2
Deionized water	-	q.s.-100	-	q.s.-100	-	q.s.-100
Total (% by						
weight)	100.0	100.0	100.0	100.0	100.0	100.0
Type of	oleaginous	o/w	olea-	o/w	olea-	o/w
Formulation	ointment	cream	ginous	cream	ginous	cream
			ointment		ointment	

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EXAMPLE NO.	Example 27	
Drug	Nitroglycerin	
	2.0	
SLP - White		
(Soy lecithin)	4.0	4.0
Triethanolamine	0.8	0.8
Triisopropanolamine	-	-
Lactic acid	0.62	-
Citric Acid	-	0.35
Butylated hydroxytoluene	0.025	0.025
White petrolatum	87.555	9.9
Liquid paraffin	5.0	12.9
Plastibase 50W	-	-
Stearyl alcohol	-	5.0
Cetyl alcohol	-	2.1
Polyethylene Glycol 4000	-	-
Polyethylene Glycol 400	-	-
Polyoxyethylene 45 monostearate	-	4.0
Sorbitan sesquioleate	-	-
Polyoxyethylene lauryl ether	-	-
p-Chloro-m-cresol	-	0.2
Deionized water	-	58.725
Total (% by weight)	100.0	100.0
Type of Formulation	Oleaginous ointment	o/w cream



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WHAT IS CLAIMED IS:

1. A topical medicament preparation for application to the skin of a patient which contains a drug capable of passing through said skin to provide topical relief to said patient for the purpose for which said drug is to be administered, said topical medicament comprising a mixture of:

(a) at least about 1% by weight of a lecithin-containing phosphatide, the amount of lecithin in said phosphatide being about 10% to about 40% by weight; and

(b) a drug suitable for topical administration, said topical medicament providing said drug suitable for topical administration in a form to permit retention of said drug at the skin of said patient to whom said drug is being applied and protecting the skin area.

2. A topical medicament of claim 1 wherein said phosphatide is soy lecithin which contains a mixture of lecithin, other phosphatides and soy oil.

3. A topical medicament of claim 1 wherein said drug is a steroid hormone.

4. A topical medicament of claim 1 wherein said drug is a steroid hormone which is hydrocortisone.

5. A topical medicament of claim 1 wherein said drug is a sulfadiazine.

6. A topical medicament of claim 1 wherein said drug is silver sulfadiazine.

7. A method of providing a prolonged topical application of a drug which comprises administering to the skin of a patient a topical medicament of claim 1, 2, 3, 4, 5 or 6.

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INTERNATIONAL SEARCH REPORT

PCT/US81/00411

International Application No.

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.³ A61K 31/65, 31/365, 31/625

US Cl. 424/199, 229, 243

II. FIELDS SEARCHED

Minimum Documentation Searched *

Classification System

Classification Symbols

US

424/199, 229, 243

Documentation Searched other than Minimum Documentation
to the extent that such Documents are Included in the Fields Searched *III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴

Category *	Citation of Document, ¹⁴ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
X	US, A, 2,484,637, Published 11 October 1949, Mattocks et al	5-7
X	US, A, 2,791,534, Published 07 May 1957, Schödf et al	3,4,7
X	US, A, 3,062,721, Published 06 November 1962, See col. 1, lines 46-75, Grate	1-7
X	US, A, 3,957,971, Published 18 May 1976, Oleniöcz	1-7

* Special categories of cited documents: ¹⁴

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on or after the priority date claimed"T" later document published on or after the international filing
date or priority date and not in conflict with the application,
but cited to understand the principle or theory underlying
the invention

"X" document of particular relevance

IV. CERTIFICATION

Date of the Actual Completion of the International Search *

15 June 1981

Date of Mailing of this International Search Report *

14 JUL 1981

International Searching Authority *

ISA/US

Signature of Authorized Officer ¹⁶*Seared. Schenk*

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